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Design, synthesis of new gatifloxacin derivatives as antibacterial activity

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Abstract
Infectious disease-causing organisms are known as pathogens. They consist of viruses, fungi, bacteria, and parasites. Quinolones function by preventing either bacterial gyrase or topoisomerase IV from acting. A series of oxadiazole derivatives was added to the antibacterial fluoroquinolone gatifloxacin to increase bulkiness at the C7 piperazine ring. The present study employed 2D FT-IR and 1H-NMR spectroscopy, as well as physical and chemical parameters like melting points, to characterize the synthesized compounds. The antibacterial activity of the compounds was tested against Gram-negative bacteria, specifically Aeruginosa pseudomonas. The tested compounds demonstrated no inhibition of the bacteria used in the research. The final synthetic chemicals' affinity for the topoisomerase IV enzyme was demonstrated by docking research. The results of this investigation demonstrated that the gatifloxacin-derived compounds had no effect on the activity of the bacteria employed in the investigation.

Keywords: 1H-NMR spectroscopy, 2D FT-IR, antibacterial activity, gatifloxacin-derived

Introduction
Today's major global issue is emerging bacterial resistance to most anti-bacterial antibiotics. Many researchers around the world are working to create new anti-biotics to combat the emerging types of bacteria that are resistant to most anti-biotics [1]. The widespread and careless use of these chemicals is associated with the issue of antibiotic resistance (AR); however, reducing the processes of developing new medications for financial reasons contributes to these factors that support AR. Numerous studies have shown that using these drugs causes the emergence and spread of AR bacterial strains [2]. The definition of infection is the entry of pathogenic organisms into the bodily tissues of a host, the organisms' reproduction, and the host tissues' reaction to the organisms and the toxins they produce [3]. A number of the most dangerous diseases for human societies are infectious ones [1].

One of the most widely used and potent anti-gram negative and positive drugs in both human and veterinary medicine are fluoroquinolones. In *E. Coli* isolates from the United Kingdom, fluoroquinolone resistance (FR) rose from 6% in 2001 to 20% in 2006. Between 2005 and 2012, there was a consistent rise in FR in Italy for Klebsiella pneumonia, with percentages ranging from 11% to 50% [4]. Certain studies suggest that fluoroquinolones, including ciprofloxacin, alatrofloxacin, grepafloxacin, gemifloxacin, and moxifloxacin, alter cytokine synthesis and release. This suggests that substances have the ability to act as anti-inflammatory and antibacterial agents [5, 6]. Fluoroquinolone has the ability to affect both gram-positive and gram-negative bacteria, including *E. Coli*, Klebsiella, Serratia, and Pseudomonas aeruginosa, as well as anaerobic Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium. And has a broad antibacterial spectrum [7, 8].

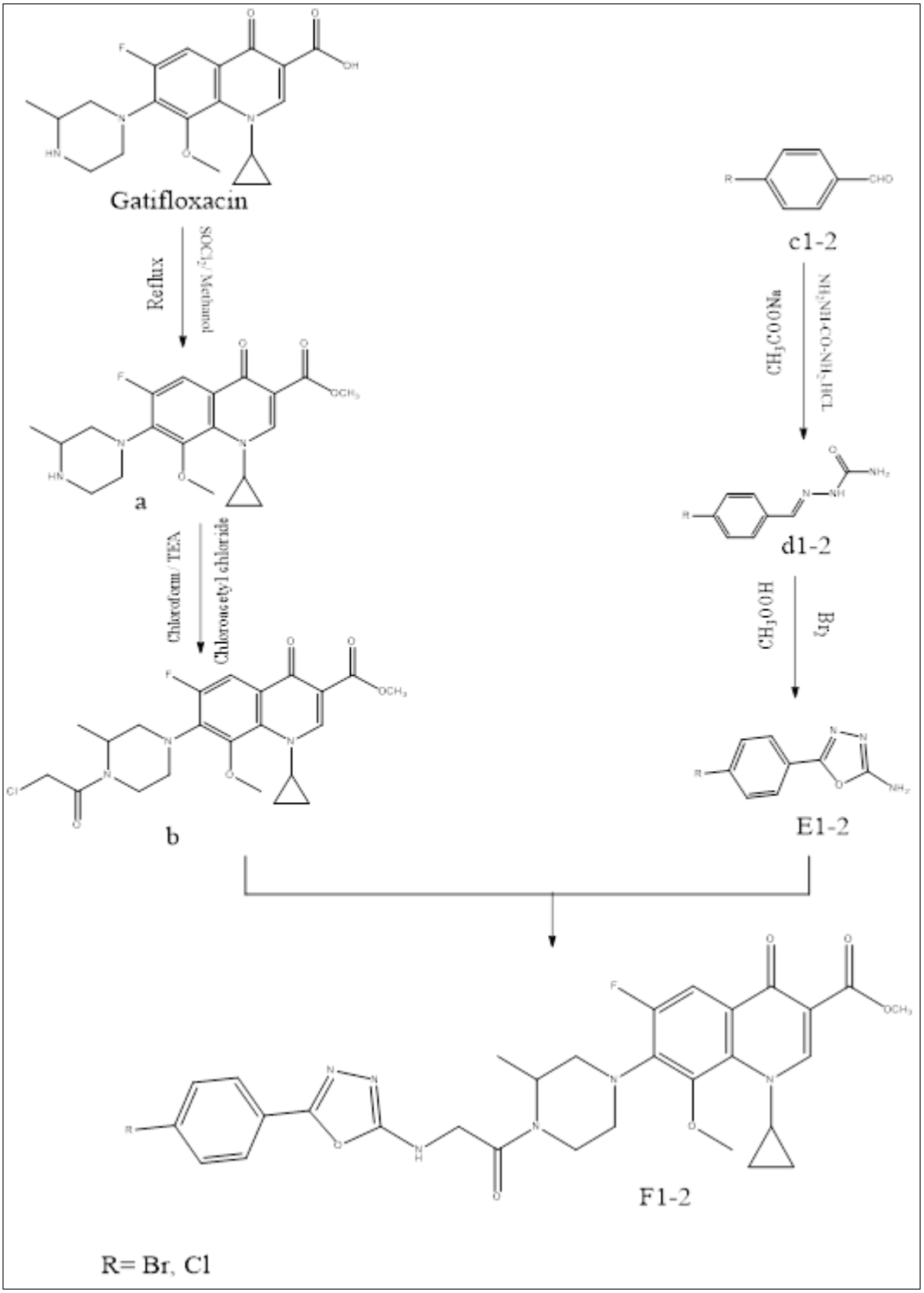
Pseudomonas aeruginosa is one opportunistic pathogen that is Gram-negative and helpful for researching virulence and bacterial social behavior. Immunocompromised and chronically ill people are more susceptible to infections, which can be difficult to treat due to the organism's tendency to form multicellular biofilms and various mechanisms for antibiotic resistance [9].

Material and Methods
Analytical-grade materials from (China, India, Spain, and the United States) were used for all reagents and anhydrous solvents. The melting points were discovered using the electro-

thermal capillary tube method. At Karbala University, KBr discs were used as the spectrum measurement tool in an FTIR spectrophotometer to measure the infrared spectrum. The 1HNMR spectra were obtained at Iran's Mashahd University. Device from Bruker using the 500 MHz-Avanc technology and DMSO as the solvent.

Chemical Synthesis

The methodologies indicated in Scheme (1) were used to manufacture the target compounds (A-F_1-2) and their intermediates.

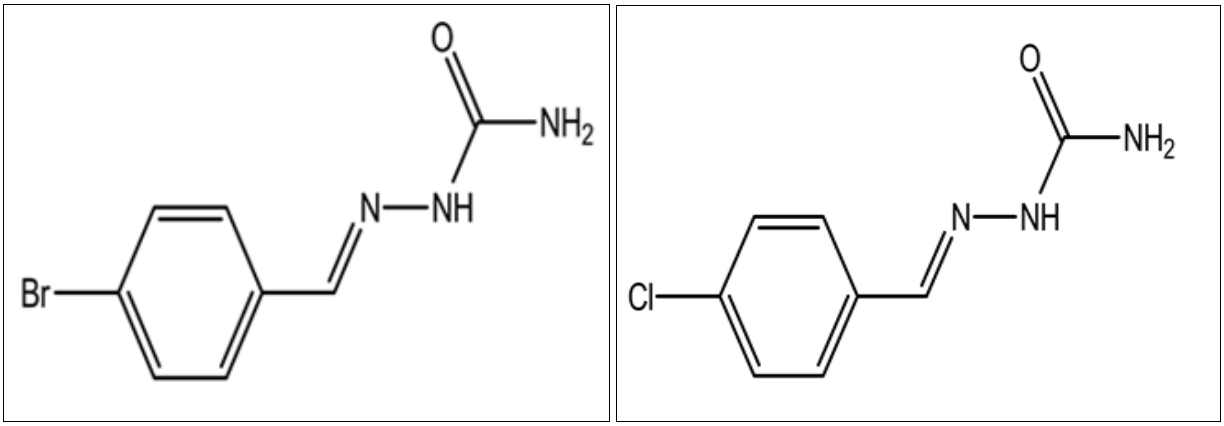


Schem 1: Synthesis of intermediates and target compounds

Semicarbazone Compounds (D $_{1\text{-}2}$) Synthesis [10]

Hal brazzide the necessary aldehydes (9 mmol) were gradually added to the mixture of hydrochloride (8 mmol, 10.89 gm.) and sodium acetate (CH_3COONa) (12 mmol, 1.23 gm.) in (35 mL) of D.W. (distilled water). The precipitate was filtered, dried, and recrystallized from 95% ethanol after stirring for an hour. The FT-IR (KBr, cm^{-1}) results for 2 - (4-bromobenzylidene) are as follows. 1-carboxamide hydrazine (d1) (figure 1 a): N-H amides include the primary amides 3462 and 3277, the secondary amides 3174, the C=O amide 1705, the C=N amide 1668, and the tension vibration of C-Br 829. The following FT-IR

(KBr, cm^{-1}) results of this compound that syntheses from other molecules to make new compound maybe have good biological activity for 2-(4-chlorobenzylidene) hydrazine-1-carboxamide (d2) are shown: Many different groups of chemical atoms binding to make this compound 705 for group (C-Cl stretching vibration), 3460 and 3270 for primary amide N-H, 3134 secondary amide with =CH of aromatic), 1700 for carbonyl of amide (C=O amide), and 1670 for (C=N) as the structure in figure 1 b.

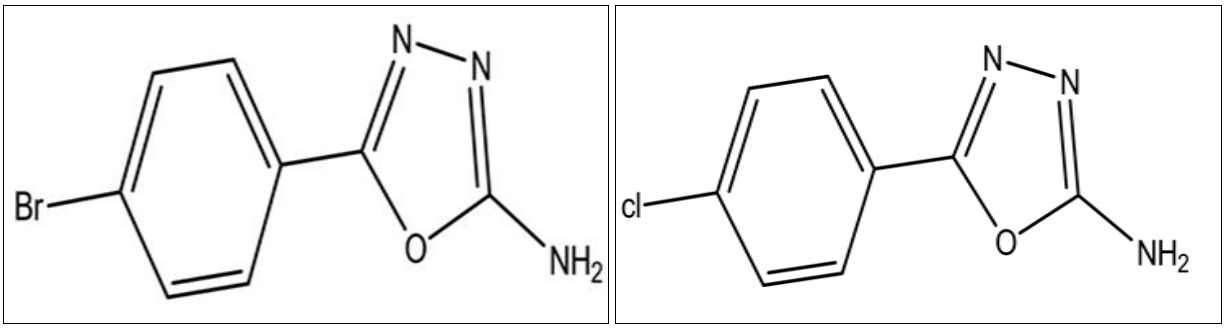


A B

Fig 1: A) Compound d1's chemical composition, B) Compound d2's chemical composition

Oxadiazole Derivatives of 2-Amino-5-Aryl-1, 3, and 4 (E_{1-2}) Synthesis [11]

Thirty milliliters of glacial acetic acid were used to dissolve sodium acetate (0.82g) and semicarbazone compounds (d1-2) (5 mmol). Next, the glacial acetic acid and bromine which dissolving in D.W to diluted it (0.7 mL in 5 mL) were added gradually. Crushed ice was added to the mixture after stirring it for an hour. The resulting solid was filtered, rinsed with cold water, dried, and then recrystallized with 95% ethanol. The structure show in figure (2 a) 5-(4-bromophenyl)-1, 3, 4-oxadiazol. The N-H primary amine results for the -2-amine (E1) FT-IR (cm^{-1}) were 3269 and 3100, the group of C=N stretching vibration was 1660, the C-O-C stretching vibration was 1114, and the C-Br stretching vibration was 831. The same manufacturing methods were used for the previous compounds, as well as filtration, drying, and purification methods for the precipitate, and the same techniques were used to diagnose the following compound.5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (E2) the result explain the atoms that binding by different types of linkage to make it, the FT-IR (cm^{-1}) show: 3302 and 3100 for the (primary amine N-H); 1660 (C=N); 1097 (C-O-C) for the stretching vibration; and the C-Cl stretching vibration was 837 the structure of compound E2 show in figure 2 b.



A) B)

Fig 2: A): Compound E1's chemical composition, B): Compound E2's chemical composition

Creation of methyl 3 methylpiperazin-1-yl-1-cyclopropyl-6-fluoro-8-methoxy-7-Compound a: 3-carboxylate, 4-oxo-1, 4-dihydroquinoline

Before adding thionyl chloride (1 mL), dropwise, to a 1.877g, 5mmol gatifloxacin solution in 50mL of pure methanol, the mixture was refrigerated to -150 C (the temperature should be maintained at -15°C). After three hours at 40 °C, for a full day, the reaction mixture was refluxed. The process involved evaporating methanol, dissolving the residual material in methanol, and then evaporating more methanol. To be sure that the complete removal of $SOCl_2$ before add the solvent (diethyl ether) to make recrystallization of the product, the procedure was repeated several times. FT-IR (KBr, cm^{-1}) peaks include those for 1520 (C=O quinolone), 1359 (C=O quinolone), the stretching vibration of piperazinyl moiety (N-H) 3430 stretching of the piperazinyl moiety), the carbon –hydrogen of aromatic ring 3080, and 2941 and stretching vibration of aliphatic carbon- hydrogen is 2900 (CH3 and CH2).

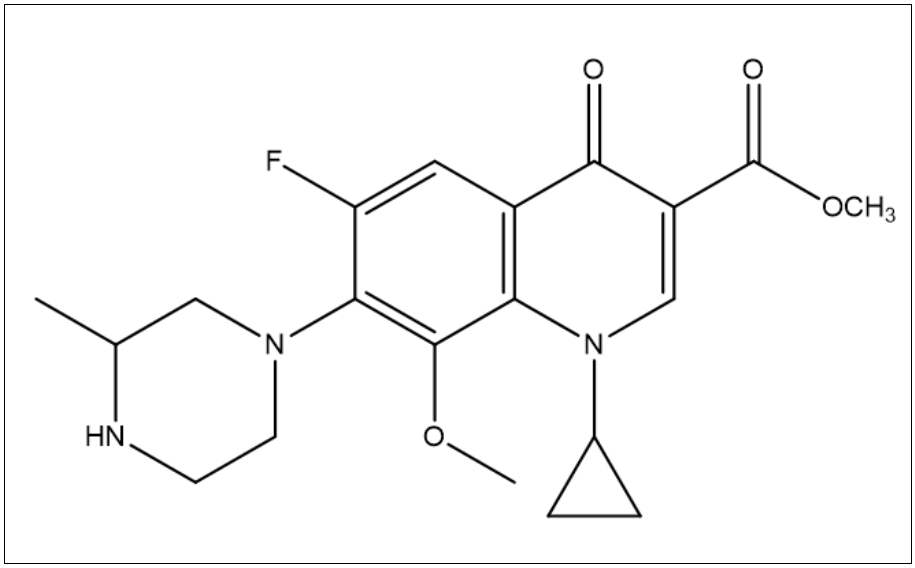


Fig 3: Compound a's chemical composition

Creation of methyl the compound b 7-(4-(2-chloroacetyl)-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoroEightmethoxy-4-oxo-1, 4-dihydroquinoline: 14 -3-carboxylate

In 30 mL of a 1:3 mixtures of DMF and chloroform, compound (b) (0.5g, 1.5 mmol) was dissolved before TEA (0.2 mL, 1.5 mmol) was added. The reaction mixture was stirred on an ice bath while 0.12 mL of chloroacetyl chloride (0.12 mL, 1.5 mmol in 10 mL of chloroform) was added dropwise and continuously stirred for an hour. This was followed by seven hours of refluxing. The precipitate was then crystallized from ethanol after the solvent had evaporated. As the other compounds were used The FT-IR (cm^{-1}) spectrum contains the following groups: the stretching vibration of carbon – hydrogen of aroematic is 3070, the vibration of C-F) is 1053, the stretching vibration of aliphatic carbon-hydrogen (C-H CH_3 and CH_2) 2940 and 2900,the carbonyl of ester (C=O ester) is1730, carbonyl of amide (C=O amide) 1650, the carbonyl of quinolone (C=O) is 1625, the stretching vibration of C-N is 1280,; and the stretching vibration of (C-Cl) 802.

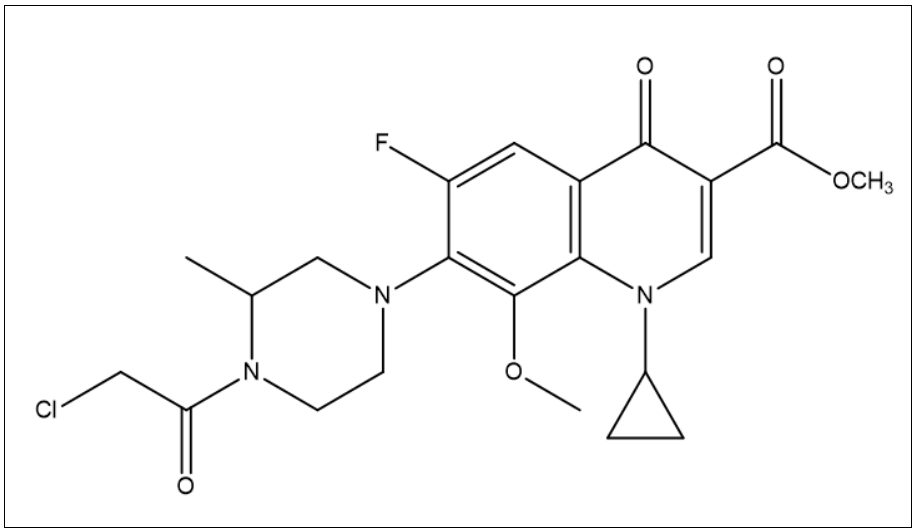


Fig 4: Compound b's chemical composition

Compound Synthesis (F_{1-2}) (Reacting in Couples)

After the compounds (E1-2) (2.12 mmol.) and (b) (1.0 g., 2.12 mmol.) were dissolved in dimethyl formamide (20.5 mL.), Triethyl amine (0.31 mL, 2.12 mmol.)All night long, the reaction mixture was stirred at ambient temperature. After the solvent was exhausted, the remaining ethanol crystallized to produce the chemicals (F_1-2). The physical data and characterisation are shown in Table (1). 4-((5-(4-bromophenyl)-1, 3, 4-oxadiazol-2-yl) glycyl) methylene7-(4) - 6 – fluoro - 8 – methoxy -1 - cyclopropyl – 1 - (3-methylpiperazin-1-yl) QUINOLINE – 4 - OXO-1, 4-DIHYDRATE () 3-carboxylate: [12-13].

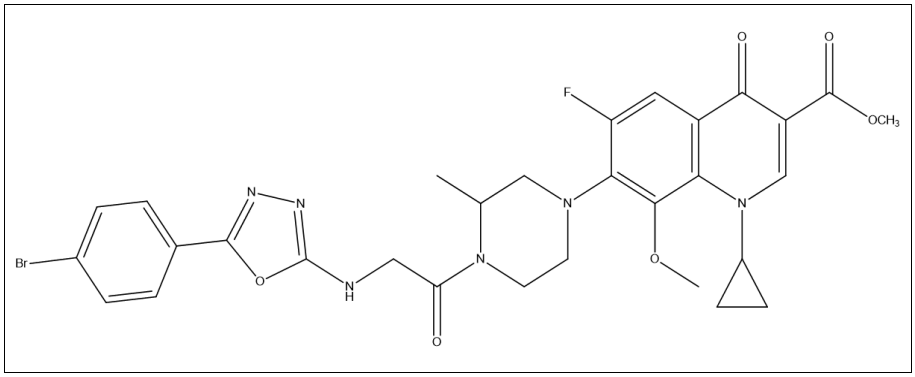


Fig 5: Compound F_1's chemical composition

FT-IR (cm^{-1}) the stretching vibration of C-F and C-Br respectively is (1170, 890),the carbonyl carbon of ester is 1730 (C=O), the carbonyl carbon of amide of quinolone 1660, 1615 (C=C stretching vibration of aromatic the following information may be found in the ppm 1H-NMR spectra: the aromatic ring show 7.70-7.73 with (4hydrogen., mlti); the CH aromatic 7.3 (2hydrogen, di); the amide is 7.30(1hydrogen, tri); 4.15 (3hydrogen, mlti and di, CH Cyclopropane CH2-NH); 3.81 (6hydrogen, s, OCH3); 3.54 (2H, d, CH2 piperazine); 1 cyclopropyl-6-fluoro-8-methoxy-4-OXO-1,4-DIHYDRATE QUINOLINEF_2: Three-carboxylate:

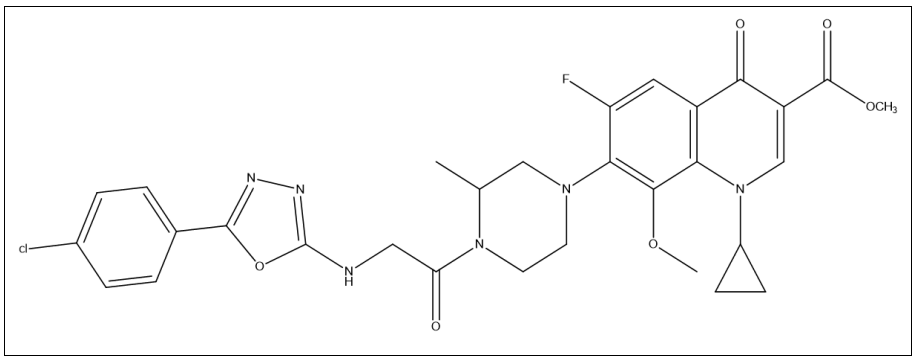


Fig 6: Compound F_2's chemical composition

Table 1: The physicochemical properties and characterisation of the produced substances

Compounds	Chemical formula	M. Wt.	Description	Melting point
F_1	$C_{30}H_{30}BrFN_6O_6$	669.5	white powder	239-241
F_2	$C_{30}H_{30}ClFN_6O_6$	625.0	white powder	252-255

3- Antibacterial study

Bacterial Isolate

A total of eight *Pseudomonas aeroginosa* bacteria were collected and diagnosed by VITK 2 Compact for identity and susceptibility test.

Only five isolate were resistance to almost all antibiotics, which were submitted to the experiment.

Pathogenic Gram-negative bacteria like Pseudomonas aeroginosa were used to test the produced compounds' *in vitro* antibacterial efficacy.

A stock solution for each compound was prepared with concentration of (2 mg/ml) by dissolve (5 mg) of compound in (10ml) of MHB (Mueller-Hinton Broth) with the aid of DMSO, and tested against isolate by tubes serial dilution method, to calculate MIC (The minimum inhibitory concentration) as flowing.

1. First tube contains (40 µg) of working solution (only MHB), a (50µg) of compound stock solution was add in eppendorf small pcr tube with well mix.
2. A (50µg) from the first tube mix was transfer to the second tube which also contain (40 µg) of working solution.
3. A (50 µg) from the second tube mix was transfer to the third tube which also contain (40 µg) of working solution.
4. A (50 µg) from the third tube mix was transfer to the fourth tube which will consider a negative control.
5. A (10 µg) of broth contain fresh cultured isolate with concentration of (0.5 MacFarland) was add to the first, second, and third tubes. Also A (50 µg) of the broth was add in fifth tube and consider as positive control.
6. Each compound was tested individually and experiment done in triple to ensure the results.
7. All tubes are incubated at 37 ºC for 24 h.
8. After 24h tubes were tested for growth to evaluate the MIC value, all data was recoded in table (2) and (3) in chapter three.

Docking study

The molecular docking technique has evolved into a critical tool in the drug creation process. This allows us to assess the interaction that happens in the study between the ligand and the protein.

Protein and ligand preparation are both required during the docking process. In MOE ligand preparation included protonation of a three-dimensional structure, energy

minimization and partial charge addition. In order to facilitate the engagement of specific ligands and receptors, the protein (2 xct) and topoisomerase enzyme II (DNA gyrase) were produced by eliminating solvent molecules (water) and other locations. Next, deleted protons were added to make it easier to upload and download the protein from the PDB. Finally, broken bonds were added and the protein molecule's potential was fixed [14].

Results and Discussion

Chemistry

The most prevalent chemical reaction that yields hydrazone compounds (Schiff base or imine) is semicarbazide and aromatic aldehyde (C1-2). Semicarbazide, a primary amine, was added by nucleophilic attack on the aromatic aldehyde's group carbonyl (C=O), which caused a proton to migrate from nitrogen (N) to oxygen (O), producing carbinolamine. Schiff bases can be created in reversible reactions with the help of catalyst acids. The iminium ion is produced when carbinolamine is protonated with oxygen through acid catalysis. However, this ion is eliminated when the hydrogen hydroxide is removed. Regeneration of the acid catalyst and loss of the nitrogen proton created the final product. Fifteen compounds (D1-2) were produced from the derivatives using controlled potential electrolysis in combination with semicarbazone electrooxidation at the bromine electrode. 1, 3, 4, and 2-amino-5-substituted oxadiazole [16].

The oxadiazole ring is created as a result of this electrochemical cyclization. The first step, called deprotonation, produces an anion that, following one electron's worth of oxidation, changes into a free radical. When the free radical experiences a second electron oxidation, a carbocation is produced. When a link between carbon and oxygen forms, the ring is complete. Finally, the process may produce 2-amino1, 3, 4, and 5-substituted oxadiazole [17].

Because the carboxyl group (OH) is frequently protected as an ester, direct nucleophilic acyl substitution of carboxylic acids in the lab is difficult and requires the transformation of the acid into an acid halide first. Consequently, it's imperative to boost the acid's reactivity, either by converting the -OH group into a better leaving group or by protonating the carboxylic group with a strong acid catalyst to make it a better acceptor. Chloroacetylchloride was used to N-acylate compound (a), resulting in compound (b). Nucleophilic acyl substitution reactions using tetrahedral intermediates transform chloroacetyl chloride into amide [18].

In contrast, there is only one electron-withdrawing group (-Cl) on the carbon in -CH2Cl. This selectivity is influenced by steric variables in addition to electronics.

The most likely location for the reaction to occur is in compound A's molecule because it also contains a free amino group. Compound A is a low basicity, strong acid. This is due to resonance's capacity to stabilize the resultant anion and the - F substitution's electron-withdrawing properties [19].

The generated heterocyclic rings (d1-2) underwent a nucleophilic substitution process (SN_2), as did the chloroacetamide derivative (b). Compound (b)'s free amino group will target chloroacetamide's ($R\text{-}CH_2\text{-}Cl$) electrophilic carbon atom. Nucleophilic substitution is the reaction between an electron pair donor (the nucleophile, Nu) and an electron pair acceptor (the electrophile). A leaving group on an sp3-hybridized electrophile is necessary for the reaction.

Pharmacology

Antibacterial research

The synthesized compounds' ($F_{1\text{-}2}$) antibacterial sensitivity test results were tested for antibacterial efficacy against gram negative bacteria: Antibiotic susceptibility of Pseudomonas aeruginosa is shown in table (2). Pseudomonas aeruginosa Isolates Pattern, and Table (3) demonstrate A: Results of product (F_1) *in vitro* activity against Pseudomonas aeruginosa isolates. B: *In vitro* activity of product (F_2) against pseudomonas aeruginosa isolates.

By catalyzing negative DNA supercoiling, DNA gyrase regulates bacterial DNA replication and transcription. Gram-negative bacteria are affected by first-generation quinolones like nalidixic acid, but some gram-positive pathogens are affected by second-generation quinolones like ciprofloxacin [15].

The reason for the compounds not inhibiting the bacteria may be that the bacteria used contain impurities or the method of isolation and purification is insufficient, or that the manufactured compound cannot inhibit them because they are resistant.

Table 2: Antibiotics susceptibility Pattern of *pseudomonas aeruginosa* Isolates.

No. Isolate	Antibiotics													
	1	**2**	**3**	**4**	**5**	6	7	8	9	10	11	12	13	14
1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	+	+	+	+	+	+	+	+	+	+	+	+	+	-
3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	+	+	+	+	+	+	+	+	+	+	+	+	+	-
6	+	+	+	+	+	+	+	+	+	+	+	+	+	-
7	+	+	+	+	+	+	+	-	I	+	+	+	-	-
8	+	+	+	+	+	+	+	-	I	+	+	+	-	-

1: Ticarcillin, 2: Ticarcillin/Clavulanic acid, 3: Piperacillin, 4: Piperacillin/Tazobactam, 5: Ceftazidime, 6: Cefepime, 7: Aztreonam, 8: Imipenem, 9: Meropenem, 10: Amikacin, 11: Gentamicin, 12: Tobramycin, 13: Ciprofloxacin, 14: Colistin, (+): Resistance، (-): sensitive I: intermediate

Table 3: Results of product (F_1) *in vitro* activity against *pseudomonas aeruginosa* isolates.

No. Isolate	1st test (mg/ml)			2nd test(mg/ml)			3rd test(mg/ml)		
	1	0.5	0.25	1	0.5	0.25	1	0.5	0.25
1	Excluded because the sample is not resistant								
2	+	+	+	+	+	+	+	+	+
3	Excluded because the sample is not resistant								
4	Excluded because the sample is not resistant								
5	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+

(+): Resistant, (-): Sensative

Table 4: Results of product (F_2) *in vitro* activity against *pseudomonas aeruginosa* isolates

No. Isolate	1st test (mg/ml)			2nd test (mg/ml)			3rd test (mg/ml)		
	1	0.5	0.25	1	0.5	0.25	1	0.5	0.25
1	Excluded because the sample is not resistant								
2	+	+	+	+	+	+	+	+	+
3	Excluded because the sample is not resistant								
4	Excluded because the sample is not resistant								
5	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+

(+): Resistant, (-): Sensative

Docking investigation

The computational docking study also used the MOE software application (Molecule Operation Environment) to conduct the docking investigations. Protooncogene topoisomerase II enzyme is the target protein (PDB ID 2 XCT). Similar to other topoisomerase inhibitors, gatifloxacin prevents the F_1 and F_2 molecules from acting. The docking of the molecular structures of F_1 and F_2 is shown in Figures (7, 8).

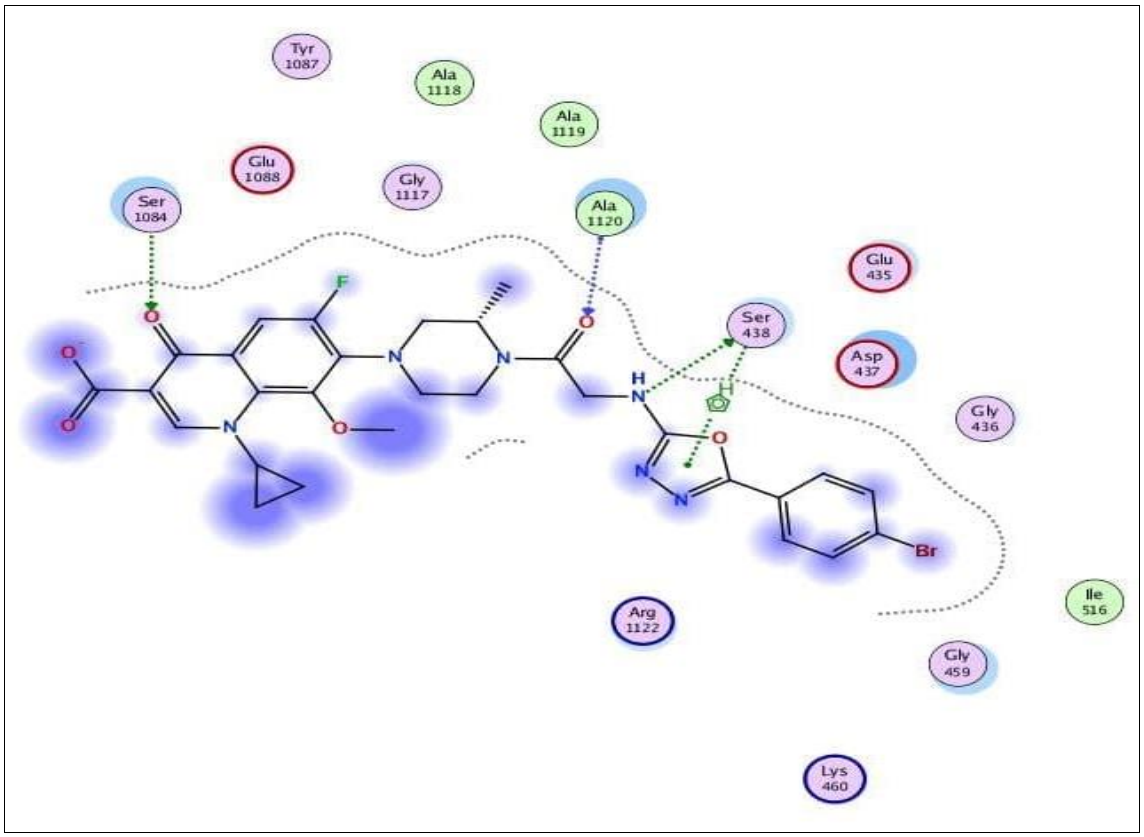


Fig 7: The F_1 molecule's (PDB code 2 XCT) chemical makeup in relation to the topoisomerase II enzyme.

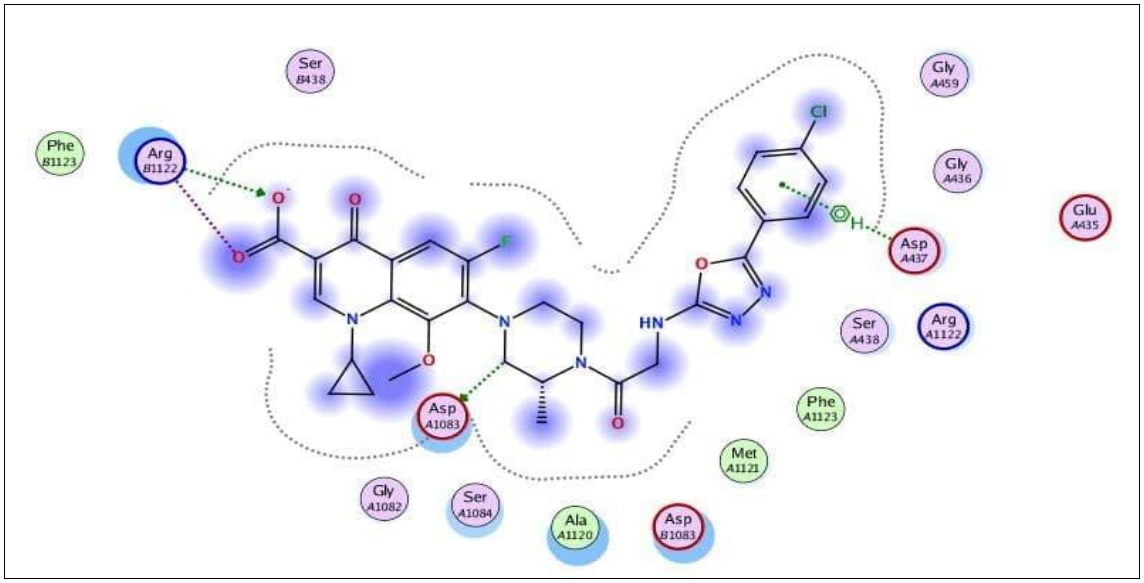


Fig 8: The F_2 molecule's (PDB code 2 XCT) chemical makeup in relation to the topoisomerase II enzyme

Conclusion

The results of this study demonstrated that the gatifloxacin-derived compounds had no effect on the activity of the bacteria employed.

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